

CLAIMS

We claim:

1. A compound of formula I,

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I

its enantiomeric, diasteromeric or tautomeric isomer, or a pharmaceutically acceptable salt thereof wherein,

10 R¹ is

- (a) Cl,
- (b) Br,
- (c) F, or
- (d) CN;

15 R² is

- (a) C₁₋₄alkyl optionally substituted by one or more OH or C₁₋₄alkoxy, or
- (b) (CH₂)_mOCH₂CH₂OH;

R³ is C₁₋₂alkyl;

20 R⁴ is a six- (6) membered heteroaryl bonded via a carbon atom having 1, 2, or 3 nitrogen atoms, wherein R⁴ is optionally fused to a benzene ring, and optionally substituted with one or more R⁶;

R⁵ is

- (a) H, or
- (b) C₁₋₂alkyl optionally substituted by OH;

25 R⁶ is

- (a) halo,
- (b) OCF₃,
- (c) cyano,
- (d) nitro,
- (e) CONR⁷R⁸,
- (f) NR⁷R⁸,
- (g) C₁₋₇alkyl, which is optionally partially unsaturated and is optionally substituted by one or more R⁹,

- (h) $O(CH_2CH_2O)_nR^{10}$,
- (i) OR^{10} , or
- (j) CO_2R^{10} ;

R^7 and R^8 are independently

- 5 (a) H,
- (b) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy,
- (c) C_{1-7} alkyl which is optionally substituted by one or more OR^{10} , phenyl, or halo substituents,
- (d) C_{3-8} cycloalkyl,
- 10 (e) $(C=O)R^{11}$, or
- (f) R^7 and R^8 together with the nitrogen to which they are attached form a het, wherein het is a five- (5), or six- (6) membered heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, or nitrogen, wherein het is optionally substituted with C_{1-4} alkyl;

15 R^9 is

- (a) oxo,
- (b) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy,
- (c) OR^{10} ,
- (d) $O(CH_2CH_2)OR^{10}$,
- 20 (e) SR^{10} ,
- (f) NR_7R_8 ,
- (g) halo,
- (h) CO_2R^{10} ,
- (i) $CONR^{10}R^{10}$, or
- 25 (j) C_{3-8} cycloalkyl optionally substituted by OR^{10} ;

R^{10} is

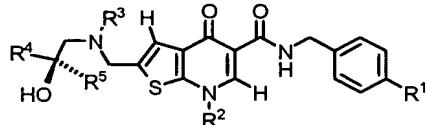
- (a) H,
- (b) C_{1-7} alkyl,
- (c) C_{3-8} cycloalkyl, or
- 30 (d) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy;

R^{11} is

- (a) C_{1-7} alkyl,
- (b) C_{3-8} cycloalkyl, or

(c) phenyl optionally substituted by halo, C₁₋₇alkyl, or C₁₋₇alkoxy;
 n is 1, 2, 3, 4 or 5; and
 m is 1 or 2.

5 2. A compound of claim 1 which is a compound of formula IA



IA.

10 wherein, R¹, R², R³, R⁴, and R⁵ are as defined according to claim 1.

3. A compound of claim 1 wherein R¹ is chloro.

4. A compound of claim 1 wherein R² is C₁₋₃alkyl.

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5. A compound of claim 1 wherein R² is methyl.

6. A compound of claim 1 wherein R² is C₁₋₃alkyl substituted with one or two hydroxy.

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7. A compound of claim 1 wherein R² is C₁₋₄alkyl substituted by C₁₋₄alkoxy.

8. A compound of claim 1 wherein R³ is methyl.

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9. A compound of claim 1 wherein R³ is ethyl.

10. A compound of claim 1 wherein R⁴ is a six- (6) membered heteroaryl bonded via a carbon atom having one (1) or two (2) nitrogen atoms.

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11. A compound of claim 1 wherein R⁴ is a six- (6) membered heteroaryl bonded via a carbon atom having one (1) nitrogen atom.

12. A compound of claims 10 wherein R⁴ is substituted with R⁶.

13. A compound of claim 10 wherein R⁴ is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyridazin-3-yl, or pyrazin-2-yl.

5 14. A compound of claim 11 wherein R⁴ is pyridin-2-yl.

15. A compound of claim 13 wherein R⁴ is pyrimidin-2-yl.

16. A compound of claim 13 wherein R⁴ is pyrazin-2-yl.

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17. A compound of claim 12 wherein R⁴ is 6-methylpyridin-2-yl.

18. A compound of claim 1 wherein R⁴ is a six- (6) membered heteroaryl bonded via a carbon atom having one (1) or two (2) nitrogen atoms and is fused to a benzene ring.

19. A compound of claim 18 wherein R⁴ is quinolin-2-yl.

20. A compound of claim 18 wherein R⁴ is substituted by R⁶.

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21. A compound of claim 1 wherein R⁵ is hydrogen.

22. A compound of claim 12 or 20 wherein R⁶ is C₁₋₄alkyl, halo, C₁₋₄alkoxy, trifluoromethyl, or NR⁷R⁸.

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23. A compound of claim 22 wherein R⁶ is methyl.

24. A compound of claim 22 wherein R⁶ is amino.

30 25. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

26. A method of treating infections by herpesviruses which comprises administering to a mammal in need thereof a compound of claim 1 or 2.
27. The method of claim 26 wherein said herpesviruses is herpes simplex virus types 1, herpes simplex virus types 2, varicella zoster virus, human cytomegalovirus, Epstein-Barr virus, human herpes virus 6, human herpes virus 7 or human herpes virus 8.
28. The method of claim 26 wherein said herpesviruses is human cytomegalovirus.
29. The method of claim 26 wherein said herpesviruses is varicella zoster virus or Epstein-Barr virus.
30. The method of claim 26 wherein said herpesviruses is herpes simplex virus types 1 or herpes simplex virus types 2.
31. The method of claim 26 wherein the compound of claim 1 is administered orally, parenterally or topically.
32. The method of claim 26 wherein the compound of claim 1 is in an amount of from about 0.1 to about 300 mg/kg of body weight.
33. The method of claim 26 wherein the compound of claim 1 is in an amount of from about 1 to about 30 mg/kg of body weight.
34. The method of claim 26 wherein said mammal is a human.
35. The method of claim 26 wherein said mammal is an animal.
36. A method of treating atherosclerosis and restenosis comprising administering to a mammal in need thereof a compound of claim 1 or 2.

37. A method for inhibiting a herpesviral DNA polymerase, comprising contacting the polymerase with an effective inhibitory amount of a compound of claim 1.

38. A compound of formula I, or a pharmaceutically acceptable salt thereof, for use
5 in the manufacture of medicines for the treatment or prevention of a herpesviral
infection in a mammal.

39. A compound of claim 1 which is

- (1) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridin-3-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (2) (+)-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridin-3-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (3) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridin-4-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (4) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (5) (+)-*N*-(4-chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (6) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-(6-methylpyridin-2-yl)ethyl)—(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (7) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-quinolin-2-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (8) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyrimidin-2-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (9) *N*-(4-chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyrimidin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (10) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (11) *N*-(4-Chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,
- (12) *N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridazin-3-ylethyl)(methyl)amino)-methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(13) *rac*-*N*-(4-chlorobenzyl)-7-ethyl-2-(((2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(14) *rac*-*N*-(4-chlorobenzyl)-7-ethyl-2-(((2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

5 (15) *rac*-*N*-(4-chlorobenzyl)-7-propyl-2-(((2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(16) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)methyl)-4-oxo-7-propyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(17) *N*-(4-chlorobenzyl)-7-(2,3-dihydroxypropyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

10 (18) *N*-(4-chlorobenzyl)-7-(3-hydroxypropyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

15 (19) *rac*-*N*-(4-chlorobenzyl)-7-(3-hydroxypropyl)-2-(((2-hydroxy-2-pyrimidin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(20) *N*-(4-chlorobenzyl)-7-(2-hydroxyethyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

20 (21) *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)methyl)-7-(2-methoxyethyl)-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(22) *N*-(4-Chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyrazin-2-ylethyl)(methyl)amino)methyl)-4-oxo-7-(2-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy)ethyl)-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

25 (23) *N*-(4-fluorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

(24) *N*-(4-cyanobenzyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide,

30 (25) *N*-(4-bromobenzyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxamide, and a pharmaceutically acceptable salt thereof.

40. A compound of claim 39 which is *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide or a pharmaceutically acceptable salt thereof.

5 41. A compound of claim 39 which is (+)-*N*-(4-chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyridin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide or a pharmaceutically acceptable salt thereof.

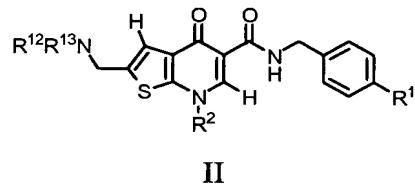
10 42. A compound of claim 39 which is *rac*-*N*-(4-chlorobenzyl)-2-(((2-hydroxy-2-pyrimidin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide, or a pharmaceutically acceptable salt thereof.

15 43. A compound of claim 39 which is *N*-(4-chlorobenzyl)-2-(((2*R*)-2-hydroxy-2-pyrimidin-2-ylethyl)(methyl)amino)methyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]-pyridine-5-carboxamide, or a pharmaceutically acceptable salt thereof.

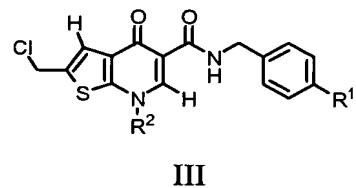
44. A method for preparing a compound of formula (I) according to claim 1 comprising:

(a) reacting an amine of a formula II,

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25 with ethylchloroformate to produce a compound of the formula III,



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and (b) reacting a compound of formula III with an amino alcohol of the formula R⁴R⁵C(OH)CH₂NH(R³) in the presence of an inorganic or tertiary amine base; wherein,

R¹ is

- (a) Cl,
- (b) Br,
- (c) F, or
- 5 (d) CN;

R² is

- (a) C₁₋₄alkyl optionally substituted by one or more OH or C₁₋₄alkoxy, or
- (b) (CH₂)_mOCH₂CH₂OH;

R³ is C₁₋₂alkyl;

10 R⁴ is a six- (6) membered heteroaryl bonded via a carbon atom having 1, 2, or 3 nitrogen atoms, wherein R⁴ is optionally fused to a benzene ring, and optionally substituted with one or more R⁵;

R⁵ is

- (a) H, or
- 15 (b) C₁₋₂alkyl optionally substituted by OH;

R⁶ is

- (a) halo,
- (b) OCF₃,
- (c) cyano,
- 20 (d) nitro,
- (e) CONR⁷R⁸,
- (f) NR⁷R⁸,
- (g) C₁₋₇alkyl, which is optionally partially unsaturated and is optionally substituted by one or more R⁹,
- 25 (h) O(CH₂CH₂O)_nR¹⁰,
- (i) OR¹⁰, or
- (j) CO₂R¹⁰;

R⁷ and R⁸ are independently

- (a) H,
- 30 (b) phenyl optionally substituted by halo, C₁₋₇alkyl, or C₁₋₇alkoxy,
- (c) C₁₋₇alkyl which is optionally substituted by one or more OR¹⁰, phenyl, or halo substituents,
- (d) C₃₋₈cycloalkyl,

(e) $(C=O)R^{11}$, or

(f) R^7 and R^8 together with the nitrogen to which they are attached form a het, wherein het is a five- (5), or six- (6) membered heterocyclic ring having 1, 2, or 3 heteroatoms selected from the group consisting of oxygen, sulfur, or nitrogen, wherein
5 het is optionally substituted with C_{1-4} alkyl;

R^9 is

(a) oxo,

10 (b) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy,
(c) OR^{10} ,

(d) $O(CH_2CH_2)OR^{10}$,

(e) SR^{10} ,

(f) NR_7R_8 ,

(g) halo,

(h) CO_2R^{10} ,

15 (i) $CONR^{10}R^{10}$, or

(j) C_{3-8} cycloalkyl optionally substituted by OR^{10} ;

R^{10} is

(a) H,

20 (b) C_{1-7} alkyl,

(c) C_{3-8} cycloalkyl, or

(d) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy;

R^{11} is

(a) C_{1-7} alkyl,

25 (b) C_{3-8} cycloalkyl, or

(c) phenyl optionally substituted by halo, C_{1-7} alkyl, or C_{1-7} alkoxy;

R^{12} and R^{13} are independently C_{1-7} alkyl, or R^{12} and R^{13} together with the nitrogen to which they are attached form morpholine, pyrrolidine, or piperidine;

n is 1, 2, 3, 4 or 5; and

m is 1 or 2.

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45. A method according to claim 44 wherein R^{12} and R^{13} together with the nitrogen to which they are attached form morpholine.

46. A method according to claim 44 wherein R¹² and R¹³ are independently methyl.

47. A method according to claim 44 wherein R¹ is chloro, R² and R³ are independently methyl, R⁴ is pyridin-2-yl, and R⁵ is hydrogen.

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48. A method according to claim 44 wherein R¹ is chloro, R² and R³ are methyl, R⁴ is pyrimidin-2-yl, and R⁵ is hydrogen.

49. N-(4-Chlorobenzyl)-2-(chloromethyl)-7-methyl-4-oxo-4,7-dihydrothieno[2,3-
10 b]pyridine-5-carboxamide.